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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,043	04/03/2000	BERND EIKMANN	21437	6651

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EXAMINER

STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/529,043

Applicant(s)

EIKMANN'S ET AL.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 March 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 91-109 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 91-106 is/are allowed.
- 6) ☒ Claim(s) 109 is/are rejected.
- 7) ☒ Claim(s) 107 and 108 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>05262005</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____. |

PD

DETAILED ACTION

Status of the Application

- [1]** Claims 91-109 are pending in the application.
- [2]** Applicants' amendment to the claims, filed 3/1/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
- [3]** Applicant's arguments filed 3/1/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [4]** The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objection

- [5]** Claims 107 and 108 are objected to as claim 107 is drawn to a vector deposited under DSM 12893, however, the deposit receipt filed 3/1/2005 indicates that DSM 12893 is a microorganism and not a vector. As such, it is suggested that claim 107 be amended to indicate that the pVWEX1pyc vector is contained in the microorganism deposited under DSM 12893.

Claim Rejection - 35 USC § 112, First Paragraph

- [6]** Claim 109 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 109 is drawn to an isolated polypeptide having at least 95% identity to SEQ ID NO:2 and having pyruvate carboxylase activity. The 95% identity limitation appears to have been entered into the specification in the amendment filed 5/20/2003. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims." As support for the 95% identity limitation, applicants cite pp. 5-9, the specific examples (pp. 10-22), and SEQ ID NO:2 as disclosed in the sequence listing (see p. 4 of the response filed 5/20/2003). However, upon review of the application as filed, the examiner can find no support for a polypeptide that has at least 95% identity to SEQ ID NO:2. MPEP § 2163 further states, "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description." Accordingly, claim 109 is rejected as not being supported by the application as filed. Applicants are invited to show support for the 95% identity limitation.

[7] The rejection of claim 109 (corresponding to claim 83 of the amended claims filed 9/2/2004) under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ [6] of the Office action mailed 11/15/2004) and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue the invention has been "more sharply defined" and the claims now presented are supported by an enabling disclosure.

Applicants' argument is not found persuasive. The examiner maintains the position that the specification, while being enabling for the isolated polypeptide of SEQ ID NO:2, does not reasonably provide enablement for all polypeptides having at least 95% identity to SEQ ID NO:2. In the previous Office action, the examiner set forth an analysis of the relevant Factors of In re Wands (see particularly pp. 6-9). Claim 84 as presented in the amendment filed 9/2/2004 is of the same scope as new claim 109 and the reasoning that applied to claim 84 now applies to claim 109. It is noted that applicants do not dispute the examiner's factual analysis of the Factors of In re Wands. While the examiner is of the opinion that this analysis is by itself sufficient to support a scope of enablement rejection, additional comments are provided below presenting a more quantitative analysis of the amount of experimentation required to make the full scope of the claimed invention.

As noted in the Office action, the scope of polypeptide variants encompasses those having a single amino acid substitution, addition, deletion, or insertion and any combination of amino acid substitutions, additions, deletions, and/or insertions up to the recited percentage identity limitation. In this case, SEQ ID NO:2 is 1140 amino acids in length. Although the claims are not limited to variants having only a single amino acid substitution with one of the 19 other common amino acids, in order to generate only single amino acid variants of each amino acid of SEQ ID NO:2, one must make 19^{1140} or 6×10^{1457} variants – just for *single amino acid variants*. Thus, at a minimum, the number of variants is 19^{1140} and the number becomes seemingly infinite when one considers that the claims broadly encompass simultaneous alteration of up to about 57

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amino acids of SEQ ID NO:2 by substitution, addition, deletion, and/or insertion. Based on this rough approximation, *the number of allowed permutations is astounding*. While methods to produce variants of a known sequence, e.g., site-specific mutagenesis and random mutagenesis, are well-known to the skilled artisan, producing variants having the desired pyruvate carboxylase activity requires that one of skill in the art know or be provided with guidance for the selection of which of the $>19^{1140}$ variants has the desired activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the $>19^{1140}$ possible variants. The reference of Guo et al. (PNAS 101:9205-9210) teaches a study suggesting that the percentage of polypeptide variants having multiple substitutions that maintain activity appears to be exponentially related by the simple formula: $(.66)^x \times 100\%$ (where x is the number of mutations introduced). As noted above, the claims broadly encompass a polypeptide that has 5% of the amino acids altered. Applying this estimate to the instant protein, 95% identity to SEQ ID NO:2 allows up to 57 mutations within the 1140 amino acids of SEQ ID NO:2 and thus only $(.66)^{57} \times 100\%$ or $5 \times 10^{-11}\%$ of random mutants having 95% identity to SEQ ID NO:2 would be active. Thus, a vast number of variants must be screened in order to isolate those variants of SEQ ID NO:2 that have the desired pyruvate carboxylase activity. Without any guidance from the specification and/or prior art, a skilled artisan is left to trial and error experimentation to determine those amino acids of SEQ ID NO:2 that can be altered without disrupting the desired pyruvate carboxylase activity. The art clearly *does not* typically engage in the screening of $>19^{1140}$ variants to isolate those relatively few ($5 \times 10^{-11}\%$) that would have the desired activity.

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As such, based on a determination by weighing all of the factual considerations of In re Wands, it is the examiner's position that the specification does not enable the claimed invention without undue experimentation.

Deposit Requirement

[8] It is noted that claim 107 (claim 108 dependent therefrom) is drawn to a novel vector contained in the microorganism deposited as DSM 12893. According to the deposit receipt filed 3/1/2005, the microorganism has been deposited under the terms of the Budapest Treaty. Further, applicants' representative has provided a statement that the deposited microorganism will be irrevocably and without restriction or condition released to the public upon the issuance of a patent (p. 6 of the instant response).

Conclusion

[9] Status of the claims:

Claims 91-109 are pending.

Claims 91-106 appear to be in a condition for allowance.

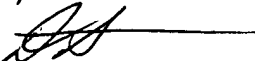
Claims 107-108 are objected to, but would be allowable if rewritten to overcome the rejection(s) set forth in this Office action.

Claim 109 is rejected, but would be allowable if rewritten to overcome the rejection(s) set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday and alternate Fridays from 7:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are

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unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (571) 273-8300. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.


DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER